REMARKS

Claims 1-16, 21-29, 31-34, and 37 are pending in the application. No amendments have been made by the present response and no new matter has been added.

35 U.S.C. §103(a) (Obviousness)

At pages 2-4 of the Office Action, claims 1-4, 6-16, 29, 32-34, and 37 were finally rejected as allegedly unpatentable over Papahadjopoulos et al, U.S. Patent No. 6,803,053 ("Papahadjopoulos") taken with Rolland et al., U.S. Patent No. 6,040,295 ("Rolland") and further in view of Lunsford et al., U.S. Published Application No. 2002/0182258 ("Lunsford"). In addition, claims 1-4, 6, 7, 9-16, 26, 29, 32-34, and 37 were finally rejected as allegedly unpatentable over Papahadjopoulos taken with Rolland and further in view of Mathiowitz et al., U.S. Patent No. 6,677,313 ("Mathiowitz"). The present Office Action stated that the rejections have been maintained, at least in part, for reasons of record in the prior Office Actions dated October 6, 2005 and February 22, 2007.

The Office Action dated October 6, 2005 stated that "it would have been obvious for one of ordinary skill in the art to employ known polymeric microparticles such as those disclosed in Lunsford to entrap and enhance the stability of the lipid:nucleic acid:PEG-DSPE complexes of Papahadjopoulos *et al.*" The Office Action dated October 6, 2005 also used substantially similar language in the obviousness rejection citing the combination of Papahadjopoulos, Rolland, and Mathiowitz.

Applicants respectfully traverse the rejection in view of the following remarks.

Independent claim 1 is directed to a microparticle that is less than about 100 microns in diameter and contains: (i) a polymeric matrix; (ii) a lipid having a pKa of less than about 2.5; and (iii) a nucleic acid molecule, wherein the microparticle is not encapsulated in a liposome and the microparticle does not comprise a cell. Independent claim 21 is directed to a microparticle that is less than about 100 microns in diameter and contains: (i) a polymeric matrix; (ii) a lipid having a pKa of less than about 2.5; and (iii) a nucleic acid molecule

Papahadjopoulos describes cationic lipid:nucleic acid complexes containing, among other components: (a) a cationic lipid; (b) a nucleic acid; and (c) a hydrophilic polymer. According to

Papahadjopoulos, the reason a hydrophilic polymer (such as polyethylene glycol distearoyl phosphatidylethanolamine; "PEG-DSPE") is incorporated into its cationic lipid:nucleic acid complexes is for the purpose of preventing the complexes from aggregating during storage and, as a result, increasing the shelf life of the complexes. The hydrophilic polymer's function in preventing aggregation of the cationic lipid:nucleic acid complexes is emphasized throughout Papahadjopoulos as an important advantage of the invention (see Papahadjopoulos at, e.g., column 13, lines 26-49, column 18, lines 32-40, and column 29, lines 30-36). This function of the hydrophilic polymer in the cationic lipid:nucleic acid complexes of Papahadjopoulos must be considered in evaluating whether the person of ordinary skill in the art would have had any reason to include the hydrophilic polymer component in the combination proposed in the Office Action.

Applicants maintain the assertion from the previous response that the skilled person would not have had any reason to entrap a PEG-DSPE-containing complex disclosed in Papahadjopoulos within a microparticle described in Lunsford or Mathiowitz.

Lunsford describes microparticles containing a polymeric matrix, a nucleic acid, and a lipid. Similarly, Mathiowitz describes microparticles containing a polymeric matrix and a nucleic acid. As noted above, the reason for including a hydrophilic polymer (e.g., PEG-DSPE) in the cationic lipid:nucleic acid complexes of Papahadjopoulos was to prevent aggregation of the complexes. The need to prevent cationic lipid:nucleic acid complex aggregation would clearly be absent if a cationic lipid:nucleic acid complex of Papahadjopoulos were to be entrapped in a microparticle of Lunsford or Mathiowitz (i.e., the cationic lipid:nucleic acid complexes would be entrapped in microparticles and thus would be unable to aggregate). Because of the particularized anti-aggregation function mediated by Papahadjopoulos's hydrophilic polymer, and the irrelevance of that function in the microparticles of Lunsford and Mathiowitz, the skilled person would have had no reason to entrap a hydrophilic polymer-containing cationic lipid:nucleic acid complex of Papahadjopoulos in a microparticle of Lunsford or Mathiowitz. Even if one were to attempt to entrap selected components (e.g., the first two components -- a cationic lipid and a nucleic acid) of a Papahadjopoulos composition in a microparticle of Lunsford or Mathiowitz, the skilled person would have had no reason to also include a hydrophilic polymer (such as PEG-DSPE) in the composition. The need to prevent

aggregation of cationic lipid:nucleic acid complexes that was the rationale for Papahadjopoulos's inclusion of a hydrophilic polymer in its complexes would be absent in Lunsford's and Mathiowitz's microparticle formulations. As a result, the skilled person would have had no reason to create the combined composition suggested in the Office Action.

In addressing applicants' previous response, the present Office Action reviewed the disclosure of the cited references and concluded the obviousness rejection by stating (at page 4) "[a]ccordingly, there is no reason not to include or substitute a hydrophilic polymer (e.g., PEG-DSPE) in the microparticle compositions" (emphasis added). Applicants respectfully submit that, contrary to the suggestion in the Office Action, obviousness is not established by the mere assertion by the Office that there is "no reason not to include" a component in a composition in the manner claimed. Rather, as the U.S. Supreme Court has stated,

> [o]ften, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit.
> *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1740-41 82 U.S.P.Q.2d 1385 (2007) (emphasis added)

The present final Office Action has suggested that it would have been obvious to select a cationic lipid:nucleic acid complex of Papahadjopoulos that includes the hydrophilic polymer PEG-DSPE and combine such a complex with a composition of Lunsford or Mathiowitz. However, in considering which of the various components of the cationic lipid:nucleic acid complexes of Papahadjopoulos to include in the proposed combination with Lunsford or Mathiowitz, a *prima facie* case of obviousness would be established only if it can be demonstrated that there was a reason to include each of the components. The person of ordinary skill in the art preparing a microparticle composition generally would not include what would have been believed to be an irrelevant component (e.g., the hydrophilic polymer PEG-DSPE) simply because there was "no reason not to" include it. Rather, the skilled person would have had to have had an affirmative reason to make the combination suggested in the Office Action. In the absence of the Office Action's identification of a reason why a person of ordinary skill in

the art would have combined the prior art elements in the manner claimed, a *prima facie* case of obviousness is clearly not established.

In view of the foregoing comments, applicants respectfully submit that the cited references do not render obvious any of claims 1-4, 6-16, 26, 29, 32-34, and 37.

At pages 4-5 of the Office Action, claims 21-24, 26-28, and 31 were finally rejected as allegedly unpatentable over Lunsford in view of Papahadjopoulos. According to the Office Action, "it would have been *prima facie* obvious for one of ordinary skill in the art to include PEG-DSPE disclosed by Papahadjopoulos *et al.* in the microparticle of Lunsford et al., with a reasonable expectation of success, to produce the microparticle of the instantly claimed invention."

Applicants respectfully traverse the rejection in view of the following comments.

As noted above, independent claims 1 and 21 are each directed to a microparticle that is less than about 100 microns in diameter and contains a polymeric matrix, a lipid having a pKa of less than about 2.5, and a nucleic acid molecule.

Lunsford describes microparticles containing a polymeric matrix, a nucleic acid, and a cationic lipid. As acknowledged in the Office Action, Lunsford does not describe including in a microparticle a lipid (such as PEG-DSPE) having a pKa of less than about 2.5. Papahadjopoulos would not have provided the skilled person any reason to include PEG-DSPE in a microparticle of Lunsford.

Papahadjopoulos describes cationic lipid:nucleic acid complexes containing, among other components: (a) a cationic lipid; (b) a nucleic acid; and (c) a hydrophilic polymer. PEG-DSPE is described by Papahadjopoulos as an example of the "hydrophilic polymer" component of its complexes, not as an example of the "cationic lipid" component. The exemplary cationic lipids listed by Papahadjopoulos (at column 11, lines 6-7) include DODAC, DOTMA, DDAB, DOTAP, DC-Chol, and DMRIE. Nowhere does Papahadjopoulos suggest that PEG-DSPE can or should be used as the cationic lipid component in its complexes. As a result, even if one were to select any one of the "cationic lipids" described by Papahadjopoulos as useable as the cationic lipid component of its cationic lipid:DNA complexes, PEG-DSPE would not have been the result of such a selection. Therefore, even if a person of ordinary skill in the art were to select a

"cationic lipid" component disclosed by Papahadjopoulos and use that cationic lipid as the cationic lipid in a microparticle composition of Lunsford, such a modification would not result in the claimed compositions.

In addition to the foregoing, and as detailed above in response to the previous obviousness rejections, Papahadjopoulos describes the inclusion of the hydrophilic polymer PEG-DSPE in its cationic lipid:nucleic acid complexes as a means to prevent aggregation of the complexes and thereby enhance their shelf life. Because this anti-aggregation function of PEG-DSPE in the complexes of Papahadjopoulos would be irrelevant in the microparticles of Lunsford, the skilled person would have had no reason to make the modification proposed in the Office Action.

In view of the foregoing comments, applicants respectfully submit that the cited references do not render obvious any of claims 21-24, 26-28, and 31.

CONCLUSION

Applicants respectfully request that all claims be allowed in view of the remarks contained herein.

Enclosed is a Petition for Extension of Time and a check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 08191-018001.

Respectfully submitted,

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